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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/066,657	02/06/2002	Daniel Javitt	A8311	5724

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EXAMINER	
KANTAMNENI, SHOBHA	
ART UNIT	**PAPER NUMBER**
1617	

DATE MAILED: 04/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/066,657	JAVITT, DANIEL	
	Examiner	Art Unit	
	Shobha Kantamneni	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 January 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *NONE* is/are allowed.

6)☒ Claim(s) *18-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment received on 01/13/2006, amended claims 22, and 23.

Claims 18-24 are pending.

Note: Applicant request for suspension of action for three months has been denied because applicant did not file a petition for such suspension.

Applicant's arguments have been fully considered but not found persuasive, the rejection of claims 18, 21 under 35 U.S.C. 112, first paragraph, as failing to comply with the **scope of enablement requirement** because the specification, while being enabling for D-serine transport inhibitors such as **D-serine dodecylamide, glycyldodecylamide, and D-alanine dodecylamide** does not reasonably provide enablement for any D-serine transport inhibitor in general in the composition for treating schizophrenia is MAINTAINED. See under response to arguments.

Applicant's arguments are persuasive, and the rejection of claims 18, and 21 under 35 U.S.C. 112, second paragraph, as being indefinite is herein withdrawn.

Applicant's arguments are persuasive, and the rejection of claims 18-24 are under 35 U.S.C. 112, second paragraph, as being indefinite is herein withdrawn.

Applicant's arguments with respect to the phrase "hydrophobic group" are persuasive, and the rejection of claims 22-23 under 35 U.S.C. 112, second paragraph, as being indefinite is herein withdrawn.

Applicant's amendment by deleting the word "inhibitor" in claims 22-24 is sufficient to overcome the rejection of claims 22-24 under 35 U.S.C. 112, second paragraph, as being indefinite due to lack of antecedent basis.

Applicant's arguments have been fully considered but not found persuasive, and the rejection of claims 20, 22-24 under 35 U.S.C. 102(b) as being anticipated by Takuma et al. (JP 08026986, PTO-892) is MAINTAINED. See under response to arguments.

Applicant's arguments have been fully considered but not found persuasive, and the rejection of claims 20, 22-24 under 35 U.S.C. 102(b) as being anticipated by Tsai et al. (WO 99/52519, PTO-892) is MAINTAINED. See under response to arguments.

Applicant's arguments have been fully considered but not found persuasive, and the rejection of Claims 18, and 21 under 35 U.S.C. 102(b) as being anticipated by Javitt (WO 97/20553, PTO-1449) is MAINTAINED. See under response to arguments.

Applicant's arguments have been fully considered but not found persuasive, and the rejection of Claim 19 under 35 U.S.C. 103(a) as being unpatentable over Javitt (WO 97/20553, PTO-1449) as applied to claims 18, and 21 above, in view of Tsai et al. is MAINTAINED. See under response to arguments.

Priority

Applicant's remarks have been fully considered with respect to the priority. It is respectfully pointed out that priority to 09/365,889 is given only to the subject matter that is already disclosed in 09/365, 889.

Applicant's are requested to point out support for the instantly claimed new subject matter in the parent application in order to complete the record. In particular, the instant application claims subject matter directed to: a composition comprising the

particular D-serine transport inhibitor such as D-serine or D-alanine compound, and the above identified U.S Appln Serial No. 09/365,889, filed August 03, 1999, now US. Patent No. 6,361,957, is directed to different subject matter: an assay method for identifying antagonists of nonsystem ASC-mediated D-serine-transport, but fails to disclose the particular compounds such as D-serine or D-alanine compound.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 18, 21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the **scope of enablement requirement** because the specification, while being enabling for D-serine transport inhibitors such as **D-serine dodecylamide, glycyldodecylamide, and D-alanine dodecylamide** does not reasonably provide enablement for any D-serine transport inhibitor in general in the composition for treating schizophrenia, rejection of record. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without undue experimentation. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required

undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547, the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1). The Nature of the Invention:

All of the rejected claims are drawn to an invention which pertains to a composition comprising an effective amount of a D-serine transport inhibitor, a pharmaceutically acceptable carrier, combined with a typical or atypical antipsychotic agent for treating schizophrenia.

(2). Breadth of the Claims:

The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims. The claims encompass compositions comprising **any** D-serine transport inhibitor, in combination with any typical or atypical antipsychiotic agent for treating schizophrenia.

(3). Guidance of the Specification / (4) Working Examples:

The specification provides compositions comprising **D-serine dodecylamide, glycyldodecylamide, and D-alanine dodecylamide** for inhibition of glycine and D-serine uptake. See page 13, Table 1.

Note that the only working example in the specification with regards to the claimed D-serine transport inhibitors shows the ability of three compounds GDA, DADA

and D-Ser-DA to inhibit glycine, D-serine uptake, and ability of these three compounds to modulate amphetamine and PCP induced effects, See page 10, lines 22-25.

(5). State of the Art:

The state of the art with regard to D-serine transport inhibitor for treating schizophrenia in **general** is underdeveloped. Different inhibitors of D-serine transport will have different chemical structures and are expected to behave in different manners, evidence that the level of skill in this art is low relative to the difficulty of the task of determining a suitable inhibitor of D-serine transport for treating schizophrenia.

(6). Predictability of the Art:

The invention is directed to a composition comprising D-serine transport inhibitors in general in combination with any atypical or atypical antipsychotic agent for the treatment of schizophrenia. It is well established that "the scope of enablement various inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839 (1970).

It is further noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. Also one skilled in the art would recognize that it is highly unpredictable with regards to not only therapeutic effects, but also side effects, and especially serious toxicity due to drug accumulation or that may be generated by drug-drug interactions when and/or after administering to a host any agents represented by either an inhibitor of D-serine transport and/or while the patient also administers other medicines. One of skill in the art would not be able to fully

predict the possible treatment of schizophrenia herein and possible adverse effects occurring with many agents having the claimed functional properties. Thus, the instant claimed invention is highly unpredictable.

(7). The Quantity of Experimentation Necessary:

In order to practice the claimed invention, one of skill in the art would have to first envision a selective D-serine transport inhibitor, an antipsychotic agent, a pharmaceutical carrier, a dosage for the inhibitor, the duration of treatment, route of treatment, etc. One of skill in the art would then need to test specific inhibitor in the model system to determine whether or not it is effective for augmenting NMDA-mediated neurotransmission, thus treating schizophrenia and one would need to test for side effects and toxicity. If the treatment is unsuccessful, one of skill in the art would have to modify the first D-serine transport inhibitor, dosage, duration of treatment, route of administration, etc. Even if successful, however, one of skill in the art would then need to determine the magnitude of the side effects and toxicity of utilizing the inhibitor. One of skill in the art would then need to determine whether or not the magnitude of the side effects could be reduced by increasing or decreasing the dosage of inhibitor while retaining the functional aspect. Once the functionality to toxicity ratio was maximized, one of skill in the art would need to determine whether or not the D-serine transport inhibitor, which had been used was of sufficient benefit that it would serve as useful for treating schizophrenia. If not, one would need to select another inhibitor, another antipsychotic agent and repeat the process until a sufficient benefit to detriment ratio had been achieved.

Genetech, 108 F.3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

The instant claims encompass **any and all compounds broadly** that would inhibit D-serine transport. The present specification lacks a structural description and/or description of other compounds encompassed by the claimed invention and, thus, does not enable the skilled artisan to make and use the claimed invention commensurate in scope with these claims.

Further, these recitations may broadly encompass those known and **unknown** compounds having the recited functions as of the instant filing date, as discussed above. Note those **future known** compounds yet to be discovered and/or made. Hence, those unknown or future known compounds encompassed by claims herein must require to additional or future research to discover, establish or verify their usefulness. Therefore, as indicated above the skilled artisan has to exercise **undue experimentation** to practice the instant invention.

Response to Arguments

Applicant's remarks that "it was known to those of ordinary skill in the art that agents which stimulated NMDA receptors via the glycine/D-serine binding site were useful in the treatment of schizophrenia" have been considered, and acknowledged herein.

Applicant's argument that "Applicant submits herewith a Supplemental Declaration under 37 C.F.R. 1.132, which establishes that based upon the present specification, one of ordinary skill in the art could readily practice the claimed invention and determine compounds within the scope of the claims for use in the claimed compositions and methods" is not persuasive because 1) the argument is not commensurate with the instant claims which are directed to the composition, and not the assay method for determining which agents fall within the broad genus, and 2) at the time of the instant invention i.e filing date of the instant application 02/06/2002, the specification merely discloses 3 compounds GDA, DADA and D-Ser-DA to inhibit glycine, D-serine uptake. Thus, the present specification at the time of the filing date 02/06/2002 does not comply with the enablement requirement because the present specification, while being enabling for D-Serine transport inhibitors such as D-serine dodecylamide, glycyldodecylamide, and D-alanine dodecylamide does not reasonably provide enablement for **any** selective D-serine transport inhibitor in general in the composition.

Applicant's arguments with respect to level of predictability in the art; the amount of direction provided by the inventor, it is respectfully pointed to the applicant's remarks on page 20 of the response that "Neither D-serine nor D-serine ethyl ester is an antagonist of D-serine transport. In this regard, Applicant refers the Examiner to the attached paper by McBain et al which demonstrates that modifications of the D-serine molecule leads to the loss of binding at the NMDA receptor". Thus from the applicant's own admission that not all D-serine compounds are D-serine transport inhibitors, it is

highly unpredictable as to which of the D-serine or D-alanine compounds would be "selective D-serine transport inhibitors". Therefore, as indicated above the skilled artisan has to exercise undue experimentation to determine the compounds that can be used in the claimed composition.

Thus, the present specification lacks a structural description and/or description of other compounds encompassed by the claimed invention and, thus, does not enable the skilled artisan to make and use the claimed invention commensurate in scope with these claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 24 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, rejection of record.

The claim recites the phrase "substituted phenyl group" The term "substituted" in the claims is vague and indefinite, as it is not clear what other compounds this term encompasses, since one of ordinary skill in the art could not ascertain the metes and bounds as to the "substituted." It is not clear if the phenyl group is "substituted" with alkyl, aryl, heteroaryl, halogen etc.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 20, 22-24 are rejected under 35 U.S.C. 102(b) as being anticipated by Takuma et al. (JP 08026986, PTO-892), rejection of record.

Takuma et al. disclose compositions containing D-serine esters preferably the ethyl ester or their pharmaceutically acceptable salts as active ingredients and pharmaceutically acceptable carrier. It is further disclosed that the compositions are useful for the treatment of schizophrenia. See abstract.

Response to Arguments

Applicant's argument that "Based upon the attached computer generated English translation of Takuma et al at paragraph [0018], the disclosed D-serine ester acts at the glycine binding site of the NMDA receptor, which is different from the claimed selective D-serine transport inhibitor of the present application" is not persuasive because Takuma et al. discloses a composition comprising a D-serine compound, D-serine ester, and further discloses that the composition therein can be used to treat schizophrenia, and thus meets the instant claims which are drawn to a composition comprising D-serine or a D-alanine compound, see claim 20.

Claim Rejections - 35 USC § 102

Claims 20, 22-24 are rejected under 35 U.S.C. 102(b) as being anticipated by Tsai et al. (WO 99/52519, PTO-892), rejection of record.

Tsai et al. disclose pharmaceutical composition containing D-alanine, D-serine or modified version of the amino acid such as salt, ester, alkylated form for the treatment of schizophrenia. See page 12, lines 26-page 13, line 30. It is further disclosed that D-serine, D-alanine can be used in combination with, or in sequence with, other antipsychotics e.g., typical or atypical and depot antipsychotics for treating schizophrenia. See page 4, lines 8-24; page 7, lines 15-19. Hydrophobically modified forms of D-serine, D-alanine such as by converting the carboxy group of the amino acid to an ester group by reaction with alcohol having 1-20 carbon atoms such as methyl, ethyl, propyl, dodecyl, phenyl etc. or by alkylation of the amino group of amino acid are also disclosed. See page 13, lines 5-25. Pharmaceutical compositions for oral administration are prepared in pharmaceutically acceptable carriers such as water or other aqueous vehicles. See page 14, lines 23-30. Thus Tsai anticipates the current invention claims 18, 20, 22-24.

Response to Arguments

Applicant's argument that "Tsai does not provide an assay for determining which agent falling within the broad genus would actually serve as an effective D-serine transport inhibitor and further, makes no mention of D-serine transport. Therefore, it cannot be said that Tsai et al anticipates the presently claimed invention" is not persuasive. It is respectfully pointed out that the argument is not commensurate with the

instant claims which are directed to the composition, and not the assay method for determining which agents fall within the broad genus, and further Tsai discloses a pharmaceutical composition containing D-alanine, D-serine or modified version of the amino acid such as salt, ester, alkylated form for the treatment of schizophrenia, and thus meets the instant claims which are drawn to a composition comprising D-serine or D-alanine compound for useful for treating schizophrenia.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 18, and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by Javitt (WO 97/20553, PTO-1449), rejection of record.

Javitt discloses a composition comprising glycyl alkyl esters, glycylalkylamides, such as glycyldodecylamide for the treatment of schizophrenia by augmenting NMDA receptor mediated neurotransmission. See page 6, lines 12-16, lines 25-27; page 9, lines 16-22; page 10, lines 15-20. It is further disclosed that glycyldodecylamide has higher potency for inhibition of glycine uptake than the esters of glycine such as glycyl ethyl ester, glycyl methyl ester, and thus more effective in treating schizophrenia. See page 17, lines 26-29. It is also disclosed that the composition comprising

glycylalkyamides can be used adjunctively with antipsychotic drugs such as haloperidol, clozapine etc. See page 10, lines 1-7. Thus Javitt anticipates instant claims 18, and 21.

Response to Arguments

Applicant's argument that "WO publication does not disclose, teach or suggest that GDA also acts as a selective D-serine transport inhibitor. On the contrary, GDA is a mixed glycine/serine transport inhibitor, whereas a selective inhibitor is claimed in the present application. This is not persuasive as it is not commensurate in scope with the instant claims. which are directed to the composition, and further Javitt discloses a pharmaceutical composition comprising glycyl alkyl esters, glycylalkylamides, such as glycyldodecylamide for the treatment of schizophrenia, and thus meets the instant claims which are drawn to a composition comprising D-serine transport inhibitor compound useful for treating schizophrenia.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over Javitt (WO 97/20553, PTO-1449) as applied to claims 18, and 21 above, in view of Tsai et al., rejection of record.

Javitt is as discussed above.

Javitt does not expressly teach a composition comprising D-alanine dodecylamide for the treatment of schizophrenia.

Tsai et al. disclose pharmaceutical composition containing D-alanine or modified version of the D-alanine such as salt, ester, alkylated form for the treatment of schizophrenia.

It would have been obvious to a person of ordinary skill in the art at the time of invention to substitute glycyl dodecylamide in the composition of Javitt with D-alanine dodecylamide because Tsai teaches D-alanine or modified version of D-alanine can be used in the composition for treating schizophrenia, and D-alanine dodecylamide is a modified version of D-alanine. One of ordinary skill in the art at the time of invention would have been motivated to substitute glycyl dodecylamide with D-alanine dodecylamide with the expectation of obtaining a pharmaceutical composition which has higher efficiency in treating schizophrenia because Tsai teaches that the dodecylamide compounds of amino acid such glycine have higher potency than esters of glycine in treating schizophrenia.

Response to Arguments

Applicant's argument "Even further, d-ala-da provided unexpectedly superior results in that it showed a different pattern of activity in the inventive assay than GDA or d-ser-da and inhibited amphetamine-induced hyperactivity whereas GDA did not. Thus, D-ala-Da would be expected to have superior efficacy relative to other compounds, which would not have been expected based upon the disclosures of Tsai and Javitt has been fully considered, but not found persuasive as discussed above in the rejection.

Conclusion

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period, will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shobha Kantamneni whose telephone number is 571-272-2930. The examiner can normally be reached on Monday-Friday, 8am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, Ph.D can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should

you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Shobha Kantamneni, Ph.D
Patent Examiner
Art Unit : 1617

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER